Optical Coherence Tomography Angiography versus Fundus Fluorescein Angiography in Assessment of Clinically Undetected Neovascularization in Severe Non-Proliferative Diabetic Retinopathy Patients

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Abstract

Background: Diabetic retinopathy is one of the most important challenges that faces the diabetic patients, simply it is a microangiopathy of the retina which leads to impairment of visual abilities if neglected, consists of many factors such as vascular walls changes and alterations in blood physiological criteria. These factors leads to capillary occlusion and so to fluid leakage and retinal ischemia.

Aim of Study: Evaluation of the superiority and sensitivity of the OCT angiography technique over fundus fluorescein angiography in detection of clinically undetected neovascularization.

Patients and Methods: Prospective, observational study. Sample consists of 30 eyes of patients presented to the outpatient clinic with severe non-proliferative diabetic retinopathy and clinically undetected neovascularizations.

Results: Results showed that FFA and OCTA were equal in diagnosing 23 eyes as Severe NPDR with no obvious proliferative activity in all retinal slabs. As well as OCTA could confirm the FFA diagnosis of suspected PDR in 6 eyes in a form of NVDs. However, OCTA was superior to FFA in diagnosing PDR and detecting neovessels (mainly NVDs) in 1 eye. In brief, this study revealed a highly significant correlation between OCT and FFA which means that OCTA shows a great utility in the clinical practice in discovering invisible neovascularization especially in the central part of the retina and to predict the progression of diabetic retinopathy, which in turn affects the management decisions and prevents unfavorable complications.

Conclusion: This study demonstrated that Conventional OCTA is very useful clinically in evaluation of new vessels formation mainly in the central retina, however FFA still owns the upper hand in assessment of proliferative activity in the peripheral retina.

Key Words: Optical coherence tomography angiography – Fundus fluorescein angiography – Diabetic retinopathy.

Introduction

DIABETIC retinopathy is a microangiopathy of the retina from which nearly all persons with diabetes eventually suffer [1].

It causes changes in the vascular wall structure and in the rheological properties of the blood. The combination of these factors leads to capillary occlusion and thereby to retinal ischemia and angiographically demonstrable leakage [2].

Early Treatment Diabetic Retinopathy Study (ETDRS) grading scheme consists of mild and moderate non-proliferative diabetic retinopathy (background diabetic retinopathy), severe non-proliferative retinopathy (pre-proliferative diabetic retinopathy) and non-high-risk and high-risk proliferative diabetic retinopathy (proliferative diabetic retinopathy) [3].

Progressing of Non-proliferative Diabetic retinopathy from mild, moderate to severe depends on the severity of flame shaped and blot haemorrhages, hard exudates, fluctuations of venous calibre (venous beading) and intraretinal microvascular anomalies [4].

As hypoperfusion in the retinal capillary bed becomes more severe and spreads across the retinal area, proliferative diabetic retinopathy develops.

Abbreviations:
NPDR : Non-Proliferative Diabetic Retinopathy.
NVD(s) : New Vessel(s) at the Disk.
OCT : Optical Coherence Tomography.
OCTA : Optical Coherence Tomography Angiography.
PDR : Proliferative Diabetic Retinopathy.
CNVM : Choroidal neovascular membranes.
FFA : Fundus Fluorescein Angiography.

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in the form of neovascularization arises at the papilla (neovascularization of the disk, NVD), on the retina outside the papilla (neovascularization elsewhere, NVE) and on the iris (neovascularization of the iris, NVI) as an attempt to compensate the ischemia [5].

For decades, dye-based angiography has been the gold standard clinical imaging modality for evaluating retinal and choroidal vascular pathologies [6].

The main idea of FFA based on injection of fluorescein dye intravenously, exciting the dye with blue light with the aid of a cobalt filter, and photographically recording the fluorescein filling sequence of the retinal vasculature [7].

One of the clear advantages of fundus fluorescein angiography is their ability to capture a much wider area of the retinal and choroidal vasculature, another advantage is that its images are less liable to show artifacts than other imaging techniques [6].

Despite its success, fundus fluorescein angiography has some weak points as being invasive and time-consuming, in addition to having the potential for allergic reactions to the dye. Moreover, it is only a two-dimensional study focusing on the superficial retinal circulation, without the ability to visualize the deeper capillary structures [6,8].

Neovascularization in proliferative diabetic retinopathy is formed by capillaries with very fragile single cell walls and may cause vitreal haemorrhages with ensuing glial proliferation, these new vessels generally appear at the edges of the ischemic areas; initially they can be recognized because they are very irregular and give rise to an intense leakage of the fluorescein [9,10].

Optical coherence tomography angiography is a relatively new, non-invasive technology that has revolutionized imaging of the retinal and choroidal microvasculature, a convenient cross-sectional and three-dimensional display [11,12].

It provides a highly-detailed, depth-resolved angiographic representation of the individual retinal capillary plexuses, facilitating qualitative and quantitative assessments of the perfusion state of the superficial, middle and deep capillary plexuses of the fovea, unobscured by leakage [6].

OCTA shows valuable practical advantages such as fast acquisition time allows images to be acquired in seconds compared to the 10-30min required by traditional dye-based angiography [11].

It is based on the detection of movement changes in moving red blood cells (Flow Motion detection) so there is no need for dye injections with their serious adverse reaction [11].

Also retinal layers segmentation one of the most precious advantages, enhancing its ability to visualize retinal neovascular lesions, such as retinal angiomatous proliferation, subretinal neovascularization and other vascular changes in type 2 macular telangiectasia, as well as choroidal lesions like CNVM and polypoidal growths [6].

The en-face acquisition areas currently range from 2 x 2mm to 12 x 12mm with the scan quality greatly decreased with a widened field of view since the same number of OCT b-scans is used for all scanning areas. Using of the montage technique allows for a larger field of view much like FA/ICGA while maintaining this improved resolution [13].

The wide-field montage OCTA image has an evident benefit in patients with Diabetic retinopathy as it allows visualization of an enlarged FAZ, perifoveal intercapillary area, and multiple microaneurysms. It also provides a larger field of view allowing more peripheral detection of microvascular changes, early NVE, and areas of capillary non-perfusion including areas too small to visualize on FA [13].

Despite being superior to dye-based angiography in some points, OCTA still has weak points and disadvantages such as being easily prone to artifacts with patient movement blinking and motion detection process, leakage not appreciated, limited imaging field precludes imaging of the retinal periphery (may be overcome with the montage image), its inability to visualize low-flow lesions [6].

Aim of the work:

Evaluation of the superiority and sensitivity of the OCT angiography technique over fundus fluorescein angiography in detection of clinically undetected neovascularization.

Patients and Methods

Methodology: Prospective, observational study.

Sample size: Sample consists of 30 eyes of diabetic patients presented to the outpatient clinic with severe non-proliferative diabetic retinopathy and clinically undetected neovascularizations.

Study setting: Ain Shams University Hospitals-Ophthalmology Department. From October 2019 – March 2021.
Study population:

Inclusion criteria: Patients with type 1 & type 2 diabetes. Patients with no clinically evident proliferative diabetic retinopathy. Naive patients with no previous injections or laser sessions.


Data collection:

Clinical examination was done to confirm the DR grading and to exclude presence of clinically obvious neovascularization. Patients underwent for FFA using Heidelberg imaging device then for OCTA imaging using the (6x6) mm scans in The AngioVue OCTA system (RTVue-XR Avanti; Optovue, Fremont, CA, USA) with a split-spectrum amplitude decorrelation angiography (SSADA) software algorithm (version 2017.1.0.49) was used. To obtain wider field images, a montage image view was performed by merging 6x6 scan of retina and 6x6 scan of disc. Comparison was done between data obtained from the two imaging techniques.

Statistical analysis:

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when parametric. Also qualitative variables were presented as number and percentages. The comparison between groups with qualitative data were done by using Chi-square test. The comparison between two groups with quantitative data and parametric distribution were done by using Independent t-test. Receiver operating characteristic curve (ROC) was used in the qualitative form to determine sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and Accuracy of FFA to predict results of OCTA. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: $p > 0.05$: Non significant. $p < 0.05$: Significant. $p < 0.01$: Highly significant.
Table (5): Correlation between FFA, type of diabetes, duration and control of disease.

<table>
<thead>
<tr>
<th>Type of diabetes:</th>
<th>FFA</th>
<th>Test</th>
<th>P-value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Severe NPDR No.=24: 7 (29.2%)</td>
<td>3 (50.0%)</td>
<td>0.938*</td>
<td>0.333 NS</td>
</tr>
<tr>
<td>Type II</td>
<td>Severe NPDR No.=17: 17 (70.8%)</td>
<td>3 (50.0%)</td>
<td>1.903</td>
<td>0.067 NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration (Range):</th>
<th>Test</th>
<th>P-value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>FFA</td>
<td>17.54±5.00</td>
<td>13.33±4.08</td>
</tr>
<tr>
<td>Range</td>
<td>FFA</td>
<td>8-30</td>
<td>10-20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Control of disease:</th>
<th>Test</th>
<th>P-value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-controlled</td>
<td>FFA</td>
<td>13 (54.2%)</td>
<td>3 (50.0%)</td>
</tr>
<tr>
<td>Controlled</td>
<td>FFA</td>
<td>11 (45.8%)</td>
<td>3 (50.0%)</td>
</tr>
</tbody>
</table>

- p-value >0.05: Non-significant (NS).
- p-value <0.05: Significant (S).
- p-value <0.01: Highly significant (HS).

Table (6): Correlation between OCTA with age and sex.

<table>
<thead>
<tr>
<th>Age:</th>
<th>Test</th>
<th>P-value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>OCTA</td>
<td>51.04±18.36</td>
<td>42.00±11.66</td>
</tr>
<tr>
<td>Range</td>
<td>OCTA</td>
<td>23-74</td>
<td>30-59</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex:</th>
<th>Test</th>
<th>P-value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>OCTA</td>
<td>12 (52.2%)</td>
<td>4 (57.1%)</td>
</tr>
<tr>
<td>Male</td>
<td>OCTA</td>
<td>11 (47.8%)</td>
<td>3 (42.9%)</td>
</tr>
</tbody>
</table>

Table (7): Correlation between OCTA with type of diabetes, duration and disease control.

<table>
<thead>
<tr>
<th>Type of diabetes:</th>
<th>OCTA</th>
<th>Test</th>
<th>P-value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>No proliferation No.=6: 6 (26.1%)</td>
<td>4 (57.1%)</td>
<td>2.329*</td>
<td>0.127 NS</td>
</tr>
<tr>
<td>Type II</td>
<td>No proliferation No.=17: 17 (73.9%)</td>
<td>3 (42.9%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration (Range):</th>
<th>OCTA</th>
<th>Test</th>
<th>P-value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>OCTA</td>
<td>17.74±5.01</td>
<td>13.29±3.73</td>
<td>2.165*</td>
</tr>
<tr>
<td>Range</td>
<td>OCTA</td>
<td>8-30</td>
<td>10-20</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Control of disease:</th>
<th>OCTA</th>
<th>Test</th>
<th>P-value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-controlled</td>
<td>OCTA</td>
<td>13 (56.5%)</td>
<td>3 (42.9%)</td>
<td>0.403*</td>
</tr>
<tr>
<td>Controlled</td>
<td>OCTA</td>
<td>10 (43.5%)</td>
<td>4 (57.1%)</td>
<td></td>
</tr>
</tbody>
</table>

- p-value >0.05: Non-significant (NS).
- p-value <0.05: Significant (S).
- p-value <0.01: Highly significant (HS).

Table (8): Correlation between FFA & OCTA.

<table>
<thead>
<tr>
<th>OCTA</th>
<th>FFA</th>
<th>Test</th>
<th>P-value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe NPDR</td>
<td>No proliferation No.=23: 6</td>
<td>23</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Proliferation</td>
<td>No proliferation No.=7: 4</td>
<td>6</td>
<td>23</td>
<td>0</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TP</th>
<th>TN</th>
<th>FP</th>
<th>FN</th>
<th>Accuracy</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFA</td>
<td>6</td>
<td>23</td>
<td>0</td>
<td>1</td>
<td>96.7</td>
<td>85.7</td>
<td>100.0</td>
<td>100.0</td>
<td>95.8</td>
</tr>
</tbody>
</table>

Fig. (1): Sensitivity and specificity of FFA in relation with OCTA.
Fig. (2): Case (1): FFA demonstrates Severe NPDR (microaneurysms with IRMAs) in all phases, OCTA also confirms the diagnosis (no proliferation).

Fig. (3): Case (2): FFA demonstrates suspected proliferative activity (NVD, NVE), OCTA confirms the diagnosis and shows NVD.
Discussion

This study based on comparison between the clinical influence of FFA and OCTA in detection of clinically unsuspected neovascularization in patients with severe NPDR.

This study included 30 eyes, with FFA imaging 24 eyes showed severe NPDR with no evidence of neovessels and 6 eyes showed suspected proliferative diabetic retinopathy.

However, with OCTA imaging the 30 eyes were divided into 23 eyes which showed no proliferative activity and 7 eyes showed proliferation (6 eyes showed NVDs only, and 1 eye showed NVD with IRMAs).

This means that FFA and OCTA were equal in diagnosing 23 eyes as severe NPDR with no obvious proliferative activity in all retinal slabs.

As well as OCTA could confirm the FFA diagnosis of suspected PDR in 6 eyes in the form of NVDs.

However, OCTA was superior to FFA in diagnosing PDR and detecting neovessels (mainly NVDs) in 1 eye.

In brief, this study revealed a highly significant correlation between OCT and FFA which means that OCTA shows a great utility in the clinical practice in discovering invisible neovascularization especially in the central part of the retina and to predict the progression of diabetic retinopathy, which in turn affects the management decisions and prevents unfavorable complications Al-Khersan et al., [14].

This study is consistent with Al-Khersan et al., in the point of comparison between Conventional OCTA and FFA in identification of NVs in severe NPDR patients with high suspicion of neovascularization.

But results are contradicted as Al-Khersan et al., showed equal accuracy between OCTA and FFA in Diabetic NV identification however this study demonstrated the superiority of OCTA over FFA You et al., [15].
This study results are consistent with You et al., as they reported that OCTA could discover subtle neovascularization especially in patients with severe NPDR that expert clinicians did not suspect, but results are different in the point that this study used conventional Optovue OCTA software however You et al., depended on wide field OCTA imaging software which provided more peripheral field to judge on.

Unlike this study, You et al., just contented with color photography and didn't involve FFA to be compared with OCTA.

Also You et al., included patients from all stages of non-proliferative diabetic retinopathy (mild-moderate-severe) in their study, unlike this study which stressed only on the severe NPDR category Pan et al., [16].

This study agree with Pan et al., as they reported that conventional OCTA was very successful in close observation of neovascularization morphology in early stages of PDR over FFA and color photography.

But they are contradicted in the point that patients included in Pan et al., were already diagnosed as PDR using FFA however, this study precisely analyzed the usefulness of OCTA over FFA in diagnosing of early neovascularization formation in severe NPDR patients which will extremely reflect on the diabetic retinopathy stages classification in the future Sawada et al., [17].

This study differs than Sawada et al., in the point of diabetic retinopathy class enrolled in the study, as it focuses mainly on Severe NPDR patient before the invasion of the proliferative activity, however Sawada et al., included patients whom already diagnosed as PDR.

Also in the point of Sawada et al., larger sample size, usage of wide field softwares either in OCTA or FFA to overcome field restriction and limited results range Pichi F. et al., [18].

This study is similar to Pichi et al., in the point of comparison between clinical picture, Fundus Fluorescein angiography and OCT angiography to evaluate sensitivity and superiority in NV identification and results were almost convenient as OCTA was superior and showed higher detection rate.

However they are contradicted as Khalid et al., enrolled patients already diagnosed as PDR and didn't consider comparison with FFA.

This study results were consistent with de Carlo et al., as they reported that conventional optovue OCTA could visualize preretinal neovascularization and IRMAs weren't apparent with clinical examination.

However, they are contradicted as de Carlo et al., enrolled patients already diagnosed as PDR and didn't consider comparison with FFA Enders et al., [21].

This study is similar to Enders et al., as they compared between OCTA and FFA in evaluation of neovascularization.

But they are contradicted as Enders et al., enrolled patients already diagnosed as PDR and depended on Zeiss angioplex OCTA.

Limitations:
The main obstacle that faced this study represented in the restricted field obtained from conventional OCTA softwares in comparison with the wider field of FFA which provides a broad surface area of the peripheral retina to evaluate, which prohibited the precise judgment on the neovascularization elsewhere (NVE) were found in the periphery.

Conclusion:
This study demonstrated that Conventional OCTA is very useful clinically in evaluation of new vessels formation mainly in the central retina, however FFA still owns the upper hand in assessment of proliferative activity in the peripheral retina.
2798 OCTA Vs FFA in Diabetic Retinopathy


مقارنة ما بين التصوير المقطعي للأوعية الدموية بالأشعة التش另外一个ية وتصوير الأوعية الدموية بالأشعة التش另外一个ية باستخدام صبغة الفلوريسين في تقنيم الأوعية الدموية غير المكتشفة بالفحص الإكلينيكى في مرضى اعتلال الشبكية السكرى غير التكاثري cad

المقدمة: اعتلال الشبكية السكرى من أمراض التحول التي تواجه مرضى السكرى، فهو ببساطة اعتلال الأوعية الدقيقة في شبكية العين.

وإهمال يؤدي إلى مضاعفات أخيرة تصل إلى حد فقدان البصر، وتكون من العديد من العوامل مثل ثبات جذور الأوعية الدموية والتهابات في العضلات الفسيولوجية للدم. تؤدي هذه الالتهابات إلى انسداد الأوعية الدموية وبالتالي تسرر السوائل ونقص تروية الشبكية.

يتسم اعتلال الشبكية السكرى بالاعتلال غير التكاثري (خفيف - متوسط - شديد) واعتلال الشبكية التكاثري وفقاً للكمية التي تحدث شبكية العين ودرجة نقص التروية وكتل الأوعية الدموية الجديدة.

لتعرض نقص التروية الناتج عن انسداد الأوعية الدموية يتضمن نقص تدفق الدم الذي يغزو جزءًا كبيرًا من الأوعية الدموية جانبية كمحاولة لتنشيط نقص إمداد الدم في منطقة ما حول العصب البصري ومناطق الشبكية المختلفة وهذا يتحول اعتلال غير تكاثري إلى اعتلال تكاثري.

تصوير الأوعية الدموية باستخدام صبغة في طريقة التصوير الإكلينيكى لقياس أمراض الأوعية الدموية بالأشعة التش另外一个ية مشيمية عين والتي تتم على حقن صبغة الفلوريسين في الوريد، وإثارة الصبغي بالضوء الأزرق. ويمكن تصوير شبيهات لفائف الفلوريسين في الأوعية الدموية في شبكية العين.

التصوير المقطعي للأوعية الدموية بالأشعة التش另外一个ية، تقنية حديثة أجريت كجزء من تصوير الأوعية الدموية الدقيقة للأشعة التش另外一个ية، وتشمل مفاصلاً وثانياً البناء لضفائر الأوعية الدموية المتخصصة والمتجددة، يمكنها تنفيذ تأثير ارتفاع مناشفة في الشبكية.

الهدف من الدراسة: أجريت هذه الدراسة على 30 مصاب اعتلال الشبكية السكرى بلغ جديد في تقنيه التصوير المقطعي للأوعية الدموية بالأشعة التش另外一个ية، لقياس نقص إمداد الدم باستخدام صبغة الفلوريسين في تقنيه جذور الأوعية الدموية غير المكتشفة بالفحص الإكلينيكى.

في المرضى الذين يعانون من اعتلال الشبكية السكرى غير التكاثري cad

استنادت هذه الدراسة على الفحص الإكلينيكى للأشعة التش另外一个ية لمرضى اعتلال الشبكية السكرى والتأكيد على عدم وجود أوعية دموية جديدة ونازفة.

ثم تصوير الأوعية الدموية بالأشعة التش另外一个ية باستخدام صبغة الفلوريسين لتحديد درجة اعتلال الشبكية السكرى.

النتائج: أظهرت هذه الدراسة نقص في تقنيه التصوير المقطعي للأوعية الدموية على تقنيه التصوير باستخدام صبغة الفلوريسين في اكتشاف ووجود أوعية دموية جديدة خاصة في الجزء المركزي من الشبكية والتي لم تكتشف بالفحص الإكلينيكى.

وتهدف تقنية التصوير باستخدام صبغة الفلوريسين ببعض التفاصيل في تقنيه التصوير الدموية الجديدة في اعتلال الشبكية السكرى التكاثري، ففيما يتعلق بتصوير أطراف الشبكية والتي لا تكون واضحة حتى الآن باستخدام النسج المتاحة لدينا من أجهزة التصوير المقطعي للأوعية الدموية.